Probing cortical dopamine function in schizophrenia: what can D1 receptors tell us?

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Schizophrenia is characterized by positive symptoms, negative symptoms and cognitive impairment. Positive symptoms may be related to excessive dopamine (DA) function, as suggested by the common antidopaminergic properties of antipsychotic medications, which are most effective at treating positive symptoms. Negative symptoms and impairment in higher cognitive functions are thought to be related to a dysfunction of the dorsolateral prefrontal cortex (DLPFC), possibly related to inappropriate stimulation of D1 receptors. In the last few years we have clearly demonstrated excess subcortical DA transmission and now have indirect evidence for cortical dopamine deficit. We studied 16 drug free patients with schizophrenia (7 drug naïve and 9 previously treated) and 16 matched controls, using positron emission tomography (PET) and [^{11}C]NNC 112, a novel radiotracer for PET imaging of the D1 receptor, and the n-back task, a test of working memory. We observed a significant upregulation in D1 binding in the DLPFC in patients with schizophrenia compared to controls. This increase was present in both drug naïve and previously treated patients and was regionally selective. Furthermore, the increase was correlated with poor performance on the n-back task (r^2=0.45, p=0.004). This upregulation of D1 receptors might be secondary to a sustained deficit in prefrontal DA function, as postmortem studies revealed deficits in DA innervation in the prefrontal cortex in schizophrenia.

Key words: Schizophrenia, dorsolateral prefrontal cortex, D1 receptors, dopamine, positron emission tomography

The classical dopamine (DA) hypothesis of schizophrenia proposed that hyperactivity of DA transmission was responsible for the 'positive' symptoms (hallucinations, delusions) observed in this disorder (1). This hypothesis was based on the correlation between clinical doses of antipsychotic drugs and their potency to block DA D2 receptors (2,3) and the psychotogenic effects of DA-enhancing drugs (for review see 4,5).

More recently functional brain imaging studies showed alterations in prefrontal cortex (PFC) function in schizophrenia associated with poor performance on frontally mediated cognitive tasks (for review see 6). At the same time, a wealth of preclinical studies emerged documenting the importance of prefrontal DA transmission at D1 receptors (the main DA receptors in the neocortex) for optimal PFC performance (for review see 7). Together, these observations led to a reformulation of the classical DA hypothesis postulating that the excess DA transmission is restricted to subcortical areas of the brain, rich in D2 receptors, and associated with positive symptoms of the illness, while a deficit in DA transmission at D1 receptors in the PFC might be implicated in the cognitive impairments and negative symptoms (8,9). This was supported by the lack of efficacy of D2 receptor antagonism in the treatment of negative and cognitive symptoms.

Over the last few years, the development of new brain imaging methods based on the principle of endogenous competition enabled direct measurement of DA transmission at D2 receptors in the striatum (for review see 10). These imaging studies, combined with studies of striatal [^{18}F]DOPA accumulation, have consistently demonstrated that schizophrenia is associated with increased presynaptic activity of DA neurons projecting to the striatum. Moreover, this increased activity is more prominent during episodes of illness exacerbation, and predicts fast response to antipsychotic drugs (for review see 11). Thus, the first arm of the dopaminergic imbalance hypothesis (hyperactivity in subcortical territory) has received strong support from imaging studies.

On the other hand, the second arm of this hypothesis (DA deficit in cortical projections) is still largely based on inferences from preclinical models or indirect clinical evidence. Patients with schizophrenia perform poorly on a number of tasks subserved, among others, by dorsolateral prefrontal cortex (DLPFC) circuitry (12). Postmortem (for review see 13,14) and in vivo functional studies (for review see 15) suggest alterations in the cytoarchitecture and function of the PFC in schizophrenia. Frontal lobe damage is frequently associated with lack of drive and motivation, core features of the negative symptoms domain in patients with schizophrenia (16). This DLPFC dysfunction may be related to impaired DA function. One postmortem study reported decreased DA terminals in the DLPFC in schizophrenia (17). Poor performance on working memory (WM) tasks has been associated in patients with schizophrenia with low cerebrospinal fluid (CSF) homovanillic acid (HVA), a marker for cortical presynaptic DA activity (18) and with the high activity associated polymorphism (Val allele) of the DA metabolism enzyme catechol-O-methyltransferase (COMT) gene (19). Patients with drug induced or idiopathic Parkinson's disease also present deficits on these tasks (20,21). In patients with schizophrenia, amphetamine and apomorphine administration is associated with improved performance on frontal tasks (22,23). Animal models also support this view (for

review see 14): monkeys with selective DA lesions in the DLPFC present prefrontal cognitive dysfunction reminiscent of impairments observed in patients with schizophrenia (24).

As the majority of DA receptors in the PFC are of the D1 subtype (25,26), evaluation of prefrontal D1 receptor function in schizophrenia is important to understand the relationship between prefrontal impairment and DA function in this condition. A wealth of preclinical data shows that appropriate activation of cortical D1 receptors is essential for WM processing in rodents and nonhuman primates (27-30). Iontophoretic application of D1 antagonists in the DLPFC impairs WM performance in monkeys (27). In aged monkeys and in catecholamine depleted monkeys, infusion of the full D1 agonists A77636 and SKF81297 partially reverses deficits in spatial WM (28,31).

A recent positron emission tomography (PET) study with [^{11}C]SCH 23390 reported decreased density of D1 receptors in the PFC in 17 male patients with schizophrenia compared to age matched controls. This study used V3" as an index of receptor density. This outcome measure is the ratio of binding potential in a region of interest to the non-specific binding in a region of reference. In other terms, V3" does not correct for potential between-subjects differences in nonspecific binding.

Because of the limitations of [^{11}C]SCH 23390 to study prefrontal D1 receptors with PET, our group selected the newly developed tracer [^{11}C]NNC 112 for this investigation. D1 receptors have been visualized with several radiotracers. The first PET radiotracers for the D1 receptor to be introduced were the benzazepines [^{11}C]SCH 23390 (KD = 0.4 nM) and [^{11}C]SCH 39166 (KD = 3.6 nM) (32-35). Both radiotracers displayed relatively low specific to nonspecific ratios, which impaired the accuracy of the D1 measurement in the PFC (36-38). Moreover, [^{11}C]SCH 23390 has a poor selectivity for D1 receptors, especially in the cortical region, where it also binds to 5-HT2A receptors (39). More recently, two new benzazepines have been evaluated as PET radiotracers: [^{11}C]NNC 756 (KD = 0.17 nM) and [^{11}C]NNC 112 (KD = 0.18 nM) (34,40-42). Both radiotracers provide high specific to nonspecific ratios. The disadvantage of [^{11}C]NNC 756 compared to [^{11}C]NNC 112 is a low selectivity against 5-HT2 receptors (in vitro selectivity about 20:1) (41,43). Thus, [^{11}C]NNC 112 is the best D1 radiotracer presently available (44).

METHODS

We studied with [^{11}C]NNC 112 and PET 16 patients with schizophrenia and 16 matched controls. Patients fulfilled DSM-IV criteria for schizophrenia or schizophreniform disorder (provisional confirmed on follow-up) and were off antipsychotics for at least 21 days and depot neuroleptics for one year (45). We excluded any other lifetime axis I diagnosis, including alcohol or substance abuse or dependence (with the exception of nicotine), a significant medical or neurological condition, and pregnancy.

Controls were matched for age (± 5 years), gender, race, parental socioeconomic status, and nicotine smoking. They also had to be free of any psychiatric, medical or neurological conditions. The study was approved by the Columbia Presbyterian Medical Center and New York State Psychiatric Institute Institutional Review Boards as well as the Radioactive Drug Research Committee of Columbia University.

Diagnosis was assessed with the Structured Clinical Interview for DSM-IV (SCID) (46) for patients and the SCID non-patient version (SCID-NP) for controls. Clinical assessment included the Positive and Negative Syndrome Scale (PANSS) (47).

WM assessment was performed with the n-back test during the neuroleptic free period (48). The n-back task used here requires subjects to monitor a series of letters presented sequentially on a computer screen, and to respond when a letter is identical to the one that immediately preceded it (1-back condition), the one presented two trials back (2-back), or three trials back (3-back). The n-back paradigm engages WM because it requires subjects to maintain information about the previous stimuli, as well as to manipulate this information (i.e. to make a comparison with the current stimulus). Sixty letters were presented in each condition. Each presentation lasted 500 msec, with 2500 msec intervals (blank screen). A total of 12, 10 and 10 targets were presented for the 1, 2 and 3-back conditions, respectively. The hit rate (HR) was calculated as the number of correct responses divided by the number of targets. The error rate (ER) was calculated as the number of errors divided by the number of nontargets. The adjusted HR (AHR) was calculated as HR minus ER and d' was calculated for 2- and 3-back as inv(HR) minus inv(ER), where inv is the inverse of the standard normal cumulative distribution.

Executive function was tested with the Wisconsin Card Sorting Task (WCST) in patients and controls.

Measurement of [^{11}C]NNC 112 binding potential (BP) was obtained as previously described (44) except that data were obtained on the new ECAT EXACT HR+, which provides a superior resolution compared to the ECAT EXACT 47 used in the feasibility study. Because of the slightly better reliability of BP compared with V3", and because BP, but not V3", corrects for potential between-subjects differences in nonspecific binding, BP was selected a priori as the outcome measure.

RESULTS

Sixteen patients and sixteen controls completed the study. The groups were matched for age, gender, race, parental socio-economic status and nicotine smoking. Of the 16 patients with schizophrenia, 7 patients were first episode/neuroleptic naïve, and 9 were neuroleptic free for at least 21 days (average of 164 days). In patients, PANSS

positive symptoms, negative symptoms, and general pathology subscale scores were 19 ± 7, 18 ± 6 and 34 ± 7, respectively.

There were no significant between-group differences in injected dose (ID), specific activity at time of injection (SA), plasma clearance of the parent compound, plasma [^{11}C]NNC 112 free fraction (f1), cerebellum total distribution volume and DLPFC gray matter volume.

DLPFC [^{11}C]NNC 112 BP was higher in patients (1.63 ± 0.39 mL g^{-1}) compared to controls (1.27 ± 0.44 mL g^{-1}, p = 0.03). The increase in DLPFC D1 receptors in patients with schizophrenia was also noted when V3" was used as an outcome measure. To assess the regional specificity of the upregulation of DLPFC D1 receptors in patients, distribution of [^{11}C]NNC 112 BP was also compared in other regions. Patients tended to show higher [^{11}C]NNC 112 BP compared to controls in all neocortical regions, but this difference reached significance only in the DLPFC. Striatal, limbic, paralimbic, and thalamic regions showed no change between groups.

There were no differences in DLPFC [^{11}C]NNC 112 BP between drug naïve (1.62 ± 0.53 mL g^{-1}) and previously treated patients (1.65 ± 0.53 mL g^{-1}), suggesting that the upregulation of D1 receptors in DLPFC was not a long-lasting side effect of previous neuroleptic medication. Furthermore, studies in primates documented that exposure to antipsychotic drugs induces downregulation of D1 receptors in the DLPFC (49,50).

In patients, DLPFC [^{11}C]NNC 112 BP was not associated with severity of positive or negative symptoms on the day of the scan (r^2 = 0.01, p = 0.35; r^2 = 0.10, p = 0.21, respectively).

WM assessment with n-back was obtained in 14 out of 16 patients and 15 out of 16 controls. Patients with schizophrenia performed above chance level in all three conditions (chance level would correspond to an AHR of 0), but significantly worse than control subjects. Results of the n-back were analyzed with repeated measure ANOVA, with WM load (1-, 2- and 3-back) as repeated measure and diagnosis (controls versus schizophrenics) as cofactor. There was a significant effect of WM load (p < 0.0001), and diagnosis (p = 0.003), and no significant diagnosis by load interaction (p = 0.37). No association was present between age and WM performance.

Among patients with schizophrenia, no differences were noted in AHR at any level of the test between first episode patients never previously exposed to antipsychotics (n = 7, AHR at 1-, 2- and 3-back of 0.90 ± 0.10, 0.64 ± 0.28, and 0.49 ± 0.31, respectively) and chronic patients previously treated with antipsychotics (n = 7, AHR at 1-, 2- and 3-back of 0.85 ± 0.20, 0.57 ± 0.33, and 0.52 ± 0.26, respectively).

Severity of positive, negative or general symptoms measured with the PANSS subscales were not predictive of performance at 1-back, 2-back or 3-back conditions (r^2 < 0.15, p > 0.05 for all correlations).

At WCST, patients performed worse than controls, but this difference did not reach significance: number of categories achieved was 5.0 ± 1.3 in controls and 4.0 ± 1.7 in patients (p = 0.09). Perseverative errors were 15.1 ± 10 in controls and 21.8 ± 14 in patients (n = 0.18).

We tested the hypothesis of an association between D1 receptor availability in DLPFC and n-back performance. When analyzing both groups together, we observed an association between low WM performance at 1-, 2- and 3-back and high DLPFC [^{11}C]NNC 112 BP. This effect was accounted for by the patients with schizophrenia (Figure 1). Within the control group, there was no relationship between performance on the n-back and D1 receptor availability. In patients, low performance at 2-back and 3-back were significantly associated with high D1 receptor availability. In patients, high DLPFC D1 receptor availability was associated with low 2-back AHR (r^2 = 0.31, p = 0.03) and low 3-back AHR (r^2 = 0.45, p = 0.008). Similar results were obtained using d'. In contrast, WCST performances were not correlated with D1 receptors availability (categories, r^2 < 0.01, p = 0.84; perseverative errors, r^2 < 0.02, p = 0.69).

DISCUSSION

This study suggests that [^{11}C]NNC 112 in vivo binding might be upregulated selectively in the DLPFC in drug free patients with schizophrenia, and that this upregulation is predictive of poor performance at the n-back test. The in

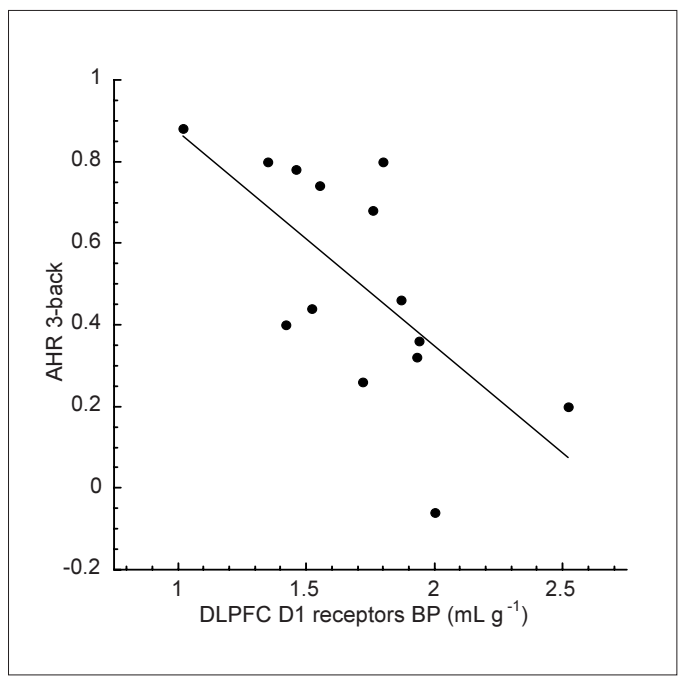

Figure 1 - Relationship between upregulation of D1 receptors in the dorsolateral prefrontal cortex (DLPFC) of untreated patients with schizophrenia and performance at working memory task (3-back adjusted hit rate, AHR; lower values represent poorer performance). BP - binding potential.

vivo binding of [11C]NNC 112 is not affected by acute changes in endogenous DA. It is therefore reasonable to assume that the increased [11C]NNC 112 binding observed in this study reflects increased concentration of D1 receptors in DLPFC of patients with schizophrenia. Our results did not replicate the findings of Okubo et al (38) of decreased [11C]SCH 23390 binding in the frontal cortex. Several factors may explain this discrepancy: the signal to noise ratio of [11C]SCH 23390 in the PFC is relatively low and may not allow reliable quantitative analysis (51). The PET camera used by Okubo et al (38) was a 7 slices device, with limited field of view and limited resolution. [11C]SCH 23390 displays a relatively low selectivity against 5-HT2A/2C receptors, and it is possible that a decrease in 5-HT2A receptors in the PFC in schizophrenia may have affected the results. Indeed, Okubo et al (52) recently reported a trend-level decrease in PFC 5-HT2A receptor density measured with [11C]NMSP in 10 previously treated patients originally included in their [11C]SCH 23390 cohort. Finally, the relationship detected in both studies between D1 binding and cognitive impairment suggest that these tracers may be detecting differentially potential receptors related trafficking changes induced by low DA tone, although in our data we have no relationship between D1 BP and performance on the WCST, suggesting that this task is less tightly related to cortical D1 function.

Due to the lack of direct measurement of presynaptic DA function in the PFC, the interpretation of this finding is inherently speculative. We postulate that an increase in DLPFC D1 receptors is a compensatory response to a deficit in presynaptic DA function. The observation that, in rodents, chronic DA depletion is associated with increased in vivo binding of [11C]NNC 112 in the PFC supports the plausibility of this interpretation of the PET findings (53). This interpretation is consistent with several other indirect lines of evidence suggesting that schizophrenia might be associated with a deficit in prefrontal DA function, and with the performance deficits at delayed-response tasks observed in nonhuman primate models of prefrontal DA deficiency. These deficits are reversed by indirect DA agonists and D1 agonists (24,28,31,54). This view is also supported by the preclinical observations that chronic phencyclidine exposure, which induces in humans symptoms reminiscent of schizophrenia (for review see 55), is associated with impaired WM performance, decreased DA turnover in the PFC (for review see 56), and upregulation of in vivo [11C]NNC 112 binding in the PFC (57). This interpretation suggests that WM function in patients with schizophrenia might be improved by DA agonists, and by the prefrontal DA enhancing effects of atypical drugs.

Our proposed model is hypothetical, and it could be argued that our findings are consistent with alternative explanations or models. The second model postulates that an increase in DLPFC D1 receptors is a primary phenomenon and the alteration in WM performance seen in these patients results from increased post-synaptic sensitivity to DA released in the DLPFC during performance of the task (58). This interpretation would predict that administration of D1 antagonists should improve WM function in patients with schizophrenia. While no studies specifically evaluated the effect of D1 receptors antagonists on WM function in schizophrenia, limited therapeutic trials with selective D1 receptor antagonists in schizophrenia showed a lack of efficacy or even worsening of clinical conditions (59-62).

Another potential model combines elements of the first and second models. This third model proposes that a persistent decrease in prefrontal DA activity might induce upregulation of D1 receptors. The upregulation could in turn lead to increased sensitivity to agonists, resulting in an overstimulation of these upregulated D1 receptors in conditions associated with DA release such as stress or cognitive challenges. This third model predicts that the 'optimal stimulation window' in schizophrenia is too narrow, and that the threshold between too little and too much D1 receptor stimulation is immediately exceeded during prefrontal DA engagement. An attractive feature of this model is that it might reconcile some apparently conflicting effects of antipsychotic drugs. By providing partial blockade at DA receptors acutely and leading to receptor downregulation chronically, antipsychotics might acutely protect against the effects of D1 receptor hyperstimulation. Raising baseline prefrontal DA activity is another mechanism by which atypical antipsychotics might correct, at least partially, the deficit in prefrontal DA that caused the problem. This model would predict that acute administration of a D1 receptor agonist alone might be detrimental, while repeated administration of a D1 agonist at low doses might lead to desensitization of the receptors and thus have long term therapeutic effects.

Proper elucidation of the role of PFC DA transmission at D1 receptors in the pathophysiology of cognitive impairment will thus critically depend not only on the development of an imaging method suitable to assess presynaptic function, but also on the development of D1 receptor agonists available for clinical investigation.

The pathogenesis of a putative deficiency in prefrontal DA function in schizophrenia is at present unknown. Elucidation of the genetic bases and mechanisms of development of the mesocortical DA system would provide important clues regarding possible origins of alterations in prefrontal DA neurons. Furthermore, alteration of DA function in schizophrenia might not be due to a primary problem of DA systems, but rather a consequence of more generalized neurodevelopmental abnormalities. However, it is an important consequence, to the extent that it is implicated in a cascade of events leading to the emergence of symptoms and persistent disability. An improved understanding of the origin of this DA phenotype will offer important leads as to potential neurodevelopmental

mechanisms that might be implicated in the illness, and open new therapeutic avenues.

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